食安発 No.0201003
February 1, 2005

To: Prefectural governors,
Mayor of designated cities, and
Mayor of special wards

Director of the Department of Food Safety[1],
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

"Basic Concept for Good Manufacturing of Foods in Tablet or Capsule Form" and "Guidelines for Self-Inspection for the Safety of Ingredients of Foods in Tablet or Capsule Form"

Since April 2003, the Committee for Reviewing the System on Health Foods had discussed the system to manage health foods. In June 2004, the committee prepared a proposal titled "How the System on Health Foods Should Be in the Future." In the proposal, about foods in a specific form, such as tablets and capsules, that helps concentrate components of the foods, the committee points out as follows: (1) "Good Manufacturing Practice (GMP) guidelines" should be prepared to ensure the homogenization of components in individual products, from the perspective of ensuring a certain level of safety, and also (2) "guidelines for ensuring the safety of ingredients" should be set out to ensure the quality of products through manufacturing process management by voluntary efforts of business operators, as well as to secure the safety of ingredients used in such foods.

In response to above, the Ministry of Health, Labour and Welfare (MHLW) has prepared two documents titled as "Basic Concept for Good Manufacturing of Foods in Tablet or Capsule Form" (Appendix 1) and as "Guidelines for Self-Inspection for the Safety of Ingredients of Foods in Tablet or Capsule Form" (Appendix 2).

These guidelines show one way of thinking to improve the effectiveness of measures for ensuring the safety of foods in tablet or capsule form. According to the concept of the guidelines and depending on the nature of the foods manufactured, the manufacturers of these food products are expected to promote voluntary efforts as the responsibility of food business operators stipulated in Article 3 of the Food Sanitation Act (Act No.233 of 1947).

The heads of prefectures, designated cities, and special wards are requested to inform the relevant sections and organizations of the guidelines to enable them to utilize the guidelines for guidance to the business operators under their own jurisdiction. The heads are also requested to make sure that necessary measures are properly implemented.

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[1] The Department of Food Safety has been renamed to the Pharmaceutical Safety and Environmental Health Bureau.

Appendix 1

Basic Concept for Good Manufacturing of Foods in Tablet or Capsule Form

I. Purpose

The Food Sanitation Act (Act No.233 of 1947) requires in Article 3 that food business operators adequately manage hygiene, in order to provide safe food products. In particular, for foods in a specific form, such as tablets or capsules (hereinafter referred to as "tablet/capsule form foods"), the quality of products should be ensured through manufacturing process management. This is because even if the safety of the ingredients has been confirmed, through manufacturing processes like concentration, components in each product may become nonhomogeneous, thereby inviting the possibility that the approved safety level is not ensured or that the expected effectiveness is not ensured.

For the management of manufacturing process, the Good Manufacturing Practice (hereinafter referred to as "GMP") for pharmaceutical products is helpful. For tablet/capsule form foods; however, GMP according to their characteristics should be introduced. Also, at this stage, it is appropriate for GMP to be introduced in a way to promote the voluntary efforts of business operators. Considering above, the basic concept for good manufacturing of tablet/capsule form foods is shown here.

Based on this concept, it is expected that business operators will manufacture such products under voluntarily compliance with GMP.

II. Target Scope

The business operators recommended to manufacture products in accordance with this basic concept are those who manufacture or process foods in various forms, including tablets, capsules, powders, liquids, that are made from chemically synthetic compounds or extracts from natural substances with a different component ratio from the original natural substances as the result of applied steps, such as fractionation, purification, or chemical reaction; or those who manufacture or process ingredients of such foods (such business operators are hereinafter referred to as "manufacturers").

Importers are expected to make efforts to ensure that the products they import are of the same quality as products manufactured in Japan. Specifically, to ensure the same product quality, the importers are expected to confirm with the manufacturers of the imports that the products were manufactured under proper manufacturing process management and to prepare documents containing relevant information, such as product information (e.g., concerning the names of ingredients and the factory) and storage methods.

III. Basic Concept

To ensure product quality, the emphasis has been thus far placed on conducting a quality test on final products. However, to conduct proper manufacturing, it is necessary to develop a system to check products at each stage of the manufacturing process, so that defective products may not appear at final stage. In other words, in the whole manufacturing process, from the receipt of ingredients to the shipment of

final products, the following two types of control operations should be systematically implemented: (1) the control focusing on manufacturing activities with mainly workforce and machinery (hereinafter referred to as “manufacturing control”) and (2) the control focusing on quality confirmation activities, such as through testing of the ingredients, intermediate products, and final products (hereinafter referred to as “quality control”).

To implement these operations, it is essential to develop management systems from the following three viewpoints.

i. Prevention of human error in each manufacturing process
ii. Prevention of product contamination and quality degradation due to the factors other than human error
iii. Ensuring a certain level of consistent quality of products throughout the whole manufacturing process

The above basic concepts can be explained as below from two aspects: (1) intangible aspects of GMP: construction of proper management organization and implementation of work control (quality and manufacturing control), and (2) tangible aspects of GMP: construction of proper structures and facilities.

(1) Development of a management organization and implementation of work control (intangible aspects of GMP)
   a. Develop an organization for manufacturing and quality control, such as installing a quality control section independent from the manufacturing section.
   b. Assign a responsible person for each section and work process to clarify the responsibility.
   c. Prepare written standard specifications and work procedures, and carry out all procedures following these documents.
   d. Check the work processes by multiple workers and record the results.
   e. Organize and retain relevant records, such as manufacturing records, storage records, and shipment records.
   f. Manage products for each lot and display product names, lot numbers, etc. on containers and main machines that are used in manufacturing.
   g. Manage hygiene, such as cleaning of work rooms and washing machines and tools, according to predetermined procedures.
   h. Always take special care for the health and sanitary conditions of workers so as not to contaminate products with microorganisms that the workers carry. Transfer them to other sections, if necessary.
   i. Restrict non-workers’ access to work rooms.
   j. Regularly check and maintain facilities, machines, and tools (including calibration of instruments).
   k. Check the quality of products at each process of manufacturing.
   l. Store specimens in an appropriate condition in preparation for the quality check after the shipment of products.
   m. Collect and utilize information, including complaints about the products, that is necessary to improve the manufacturing and quality control.

n. Perform self-inspection regularly on whether manufacturing process management is properly implemented.

o. Provide educational training systematically for all persons who are engaged in GMP operations, such as general managers, persons in charge of each section and work process, and workers.

(2) Construction of structures and facilities (tangible aspects of GMP)

a. Work rooms should have enough space and appropriate structure for the works, to ensure that, for example, in a labeling and packaging room, work tables are partitioned for each item to prevent wrong labeling, and adequate space is provided between the work tables to avoid confusion of items.

b. Contamination of products by dusts should be prevented.

c. Cross-contamination should be prevented, for example, by dedicating rooms for each work.

d. The interior of workrooms, such as the floor, wall, and ceiling, should be made from easy-to-clean materials and should be able to be disinfected as necessary.

e. For machines, tools, and containers used in the manufacturing process of products, especially, the parts that come into direct contact with products or their ingredients should be made from materials that do not affect the quality of products. Also, the machines should have a structure that does not help to contaminate products with lubricants.

f. Work rooms and machinery should be reasonably arranged according to the sequence of manufacturing processes.

g. Hand-washing facilities and dressing rooms should be installed.

IV. Implementation of Manufacturing Process Management

1. Placement of persons in charge

Manufacturers must assign a general manager for each factory to supervise the manufacturing and quality control. Under the supervision of each general manager, allocate a person in charge of manufacturing control for the relevant sections and a person in charge of quality control for the relevant sections.

Upon placing a person in charge, the following considerations should be made.

(1) The general manager must fall under any of the following items:

a. A physician, dentist, pharmacist, or veterinarian;

b. A person who has completed a course in medical science, dentistry, pharmacy, veterinary medicine, nutrition, animal science, fisheries science, agricultural chemistry or chemistry, and graduated from a university under the School Education Act (Act No. 26 of 1947), a university under the old University Ordinance (Imperial Ordinance No. 388 of 1918), or a vocational training school under the old Vocational Training School Ordinance (Imperial Ordinance No. 61 of 1903); or

c. A person who has been engaged in work related to manufacturing or quality control for not less than five years.

(2) The person in charge of manufacturing control and the person in charge of quality control must be a different person.

2. Preparation of standard documents

In order to carry out appropriate manufacturing and quality control, it is necessary to clarify the role of the organization, work procedures, product specifications, and other necessary matters. To enable everyone to play the role concerned as long as they follow the documents, manufacturers must prepare the following standard documents to specify raw materials, machines and tools, methods for manufacturing, and quality control, as well as product quality.

(1) Product standards

Standard documents that specify the characteristics of the product and its manufacturing method, and other necessary matters, to clarify the quality of the product to be secured through manufacturing process management. They must be prepared for each type of product.

(2) Manufacturing management standards

Standard documents that specify standard methods for the process management, such as manufacturing and storage of products, from the receipt of product ingredients and other materials required for production to the shipment of final products. They must be prepared for each factory.

(3) Manufacturing hygiene management standards

Standard documents that specify methods for the hygiene management of workers and of the structures and facilities, to prevent contamination of products in the manufacturing process. They must be prepared for each workplace.

(4) Quality control standards

Standard documents that specify quality control methods, such as specimen collection methods and result determination methods for tests and inspections, which are critical factors for proper quality control. They must be prepared for each factory.

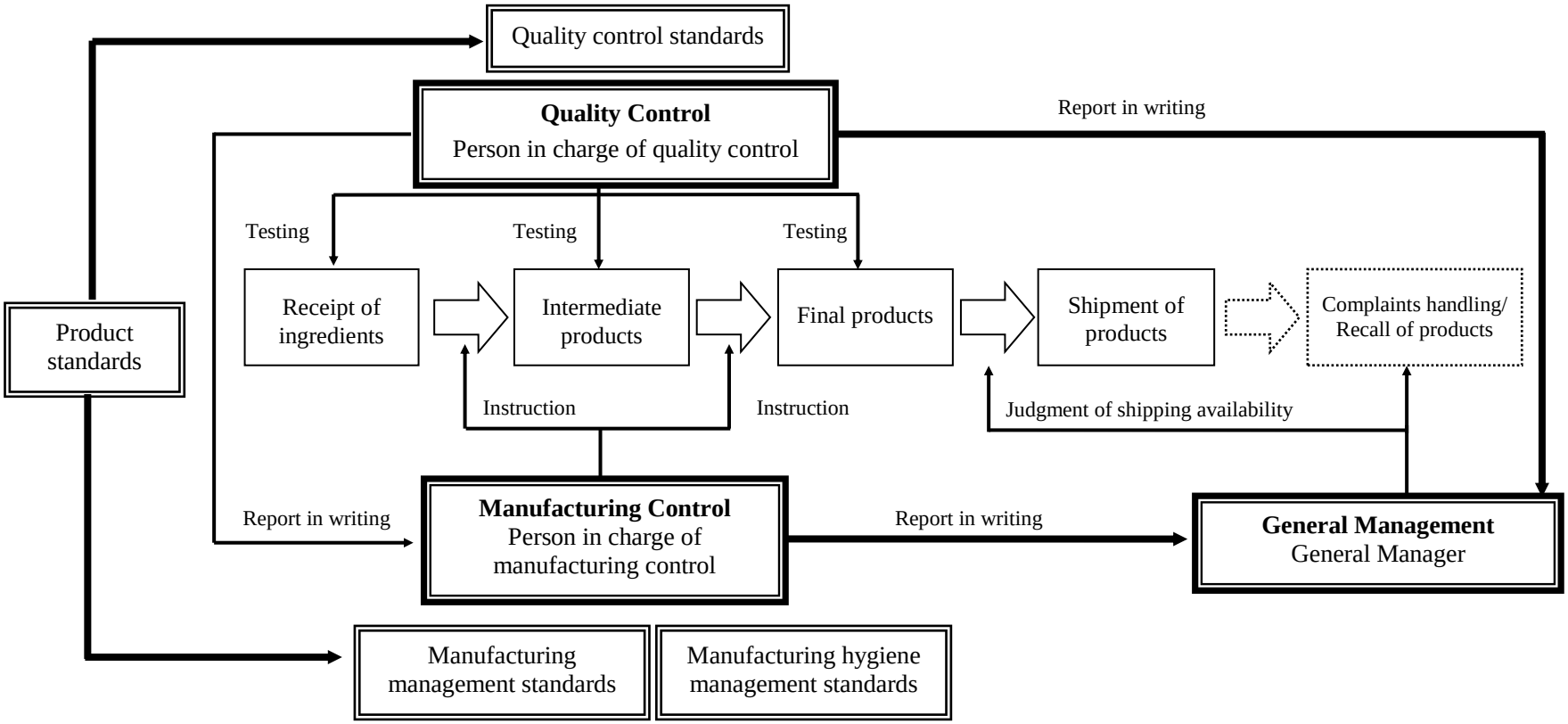
Specific details of the work of each person in charge and matters to be described in individual standard documents for the implementation of GMP should be specified according to the characteristics and actual manufacturing status of each kind of product. What is shown in the Attachment is an example of the manufacturing process management based on GMP.

V. Preparation and Retention of Records

Records should be prepared and retained appropriately, referring “Preparation and retention of records by food business operators based on the provisions of Article 1-3, paragraph (2) of the Food Sanitation Act” (Notice of the Director of the Department of Food Safety, Pharmaceutical and Food Safety Bureau, MHLW 食安発 No.0829001 of August 29, 2003).

Attachment

The Manufacturing Process Management based on GMP



Appendix 2

Guidelines for Self-Inspection for the Safety of Ingredients of Foods in Tablet or Capsule Form

I. Purpose

The Food Sanitation Act (Act No.233 of 1947) requires in Article 3 that food business operators adequately manage hygiene, in order to provide safe food products. In particular, for foods in a specific form, such as tablets or capsules (hereinafter referred to as "tablet/capsule form foods"), there is the likelihood that a minimal amount of toxic substances naturally occurring in their ingredients are concentrated in the products, together with the concentration of the ingredients. Thus, to prevent the health problems caused by excessive consumption of such products, more attention should be paid to ensuring the safety of them.

Article 3 also stipulates that ensuring the safety of ingredients is the responsibility of food business operators. Regarding the manufacturing and sales of ingredients of tablet/capsule form foods, taking account of their characteristics, voluntary efforts of business operators for ensuring safety are expected.

For the aforementioned reason, the guidelines for self-inspection procedures for the safety of ingredients of tablet/capsule form foods have been prepared.

II. Target Scope

The business operators who are recommended to perform this kind of self-inspection are those who manufacture or sell chemically synthetic compounds or extracts from natural materials but have a different component ratio from the original natural substances as the result of applied steps, such as fractionation, purification, or chemical reaction, as ingredients of processed foods in various forms, including tablets, capsules, powders, liquids; or those who manufacture processed foods in the abovementioned forms by using such ingredients or sell processed foods made from such ingredients.

III. Concept of Self-Inspection

In April 2000, the Criteria on Scope of Pharmaceuticals (Attachment of Notice of the Director-General of the Pharmaceutical Affairs Bureau[1], Ministry of Health and Welfare, *薬発* No.476, June 1, 1971: Guidance and Regulations on Unapproved/Unlicensed Pharmaceuticals) was revised. This revision led to the decision that whether a product is a pharmaceutical product or not must not be determined based only on its form, such as a tablet or capsule. In response to this, the distribution of food products in these forms has become available.

Usually, the safety of a food has been secured through a long history of consumption as food. However, there are some foods whose safety cannot be secured based only on the history of consumption. In particular, tablet/capsule form foods have possibility of

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[1] The Pharmaceutical Affairs Bureau has been renamed to the Pharmaceutical Safety and Environmental Health Bureau.

excessive consumption; it is impossible to say that such food is unlikely to cause harm to human health based only on the history of consumption.

From the above viewpoints, the guidelines set forth the following measures as basics.

1. On the original ingredients used for manufacturing ingredients, collect safety/toxicity information through documentary research.

2. For a food whose safety cannot be assured based on its history of consumption, perform toxicity tests on their ingredients.

The Attachment shows an example of procedures for a safety inspection to be conducted by business operators. The conduct of the inspection helps the operators to judge whether the manufacturing methods for ingredients of such food is appropriate or whether the marketing of the ingredients can be approved. (Refer to Attachment: Flowchart for Self-Inspection for Safety of Ingredients of Foods in Tablet or Capsule Form.)

The guidelines have been established targeting only ingredients that are used in such food to enable it to develop an expected function. It should be noted that the safety of the food cannot be assured only by conducting the safety inspection.

Attachment

Flowchart for Self-Inspection for Safety of Ingredients of Foods in Tablet or Capsule Form

Definition

1. Ingredient: Compound ingredients to manufacture processed foods that are subject to the inspection. However, substances used to formulate the compound ingredients, such as excipients, base materials, and solvent, are not included. Also, substances that are used as food additives are not included.[*1]

2. Original ingredients: Original substances used for manufacturing ingredients, such as animals and plants (defined by scientific names) or specific parts of them, microorganisms (defined by scientific name), and minerals.

   When the ingredients are chemically synthetic compounds that are not derived from living organisms, original ingredients refer to the chemical substances contained in the ingredients.

Procedures for self-inspection

STEP 1

Clarify what ingredients are used in the target product.

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STEP 2

Confirm that all the ingredients are not the ingredients (raw materials) used exclusively for drugs. (Clarify the food and pharmaceutical categories.)[*2]

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STEP 3 (Self-inspection for individual ingredients)

Clarify the methods ensuring the origin and the used parts of original ingredients, as well as the way ensuring that the manufacturing methods for the ingredients are appropriate.[*3]

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Confirm that a certain level of consistent quality of ingredients is always ensured.[*4]

↓

STEP4

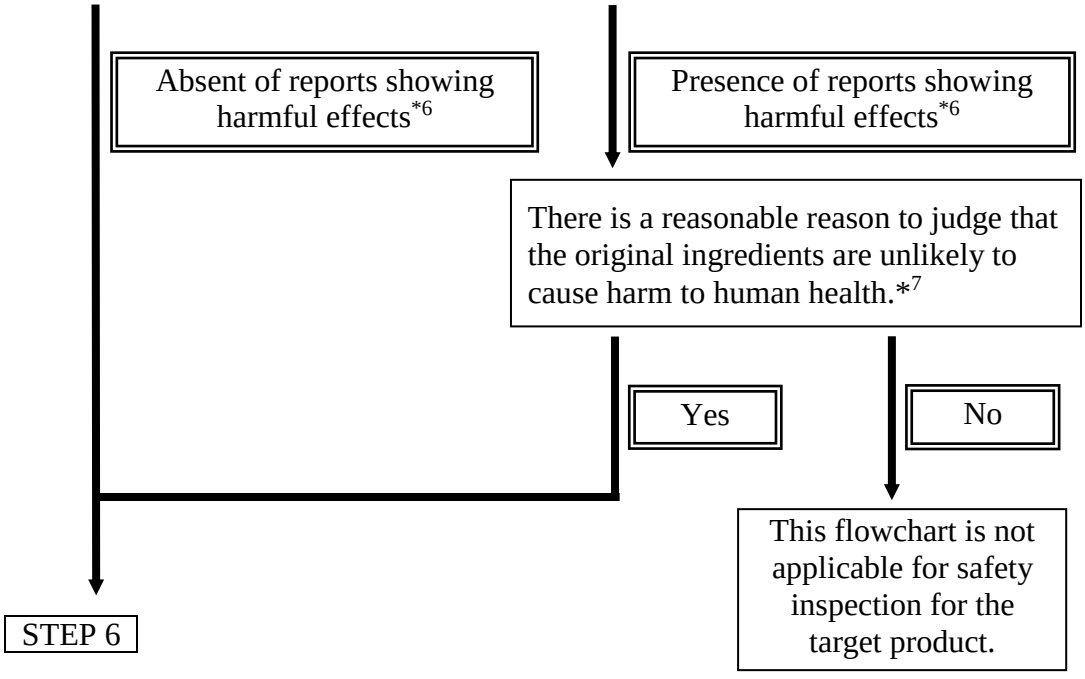
STEP 4

The ingredients used are considered equivalent to existing foods.*[5]

STEP 5

Conduct documentary research on safety information on the original ingredients.

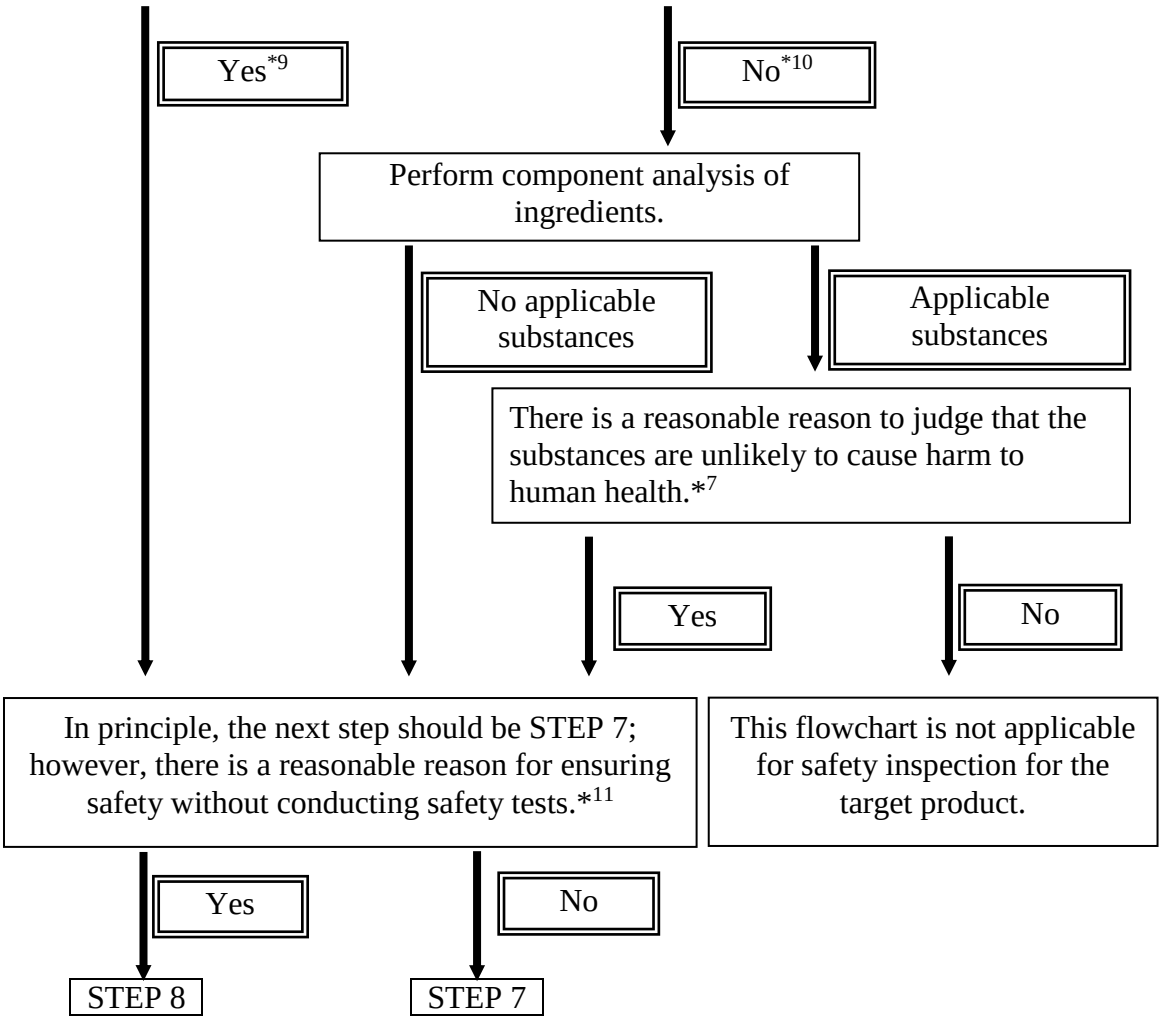
Is there safety/toxicity information (including epidemiological data) obtained from scientifically sound database of search engines, such as Chemical Abstract, PubMed, and RTECS?



STEP 6

Conduct documentary research on components contained in the original ingredients as well as the safety of the components.*8

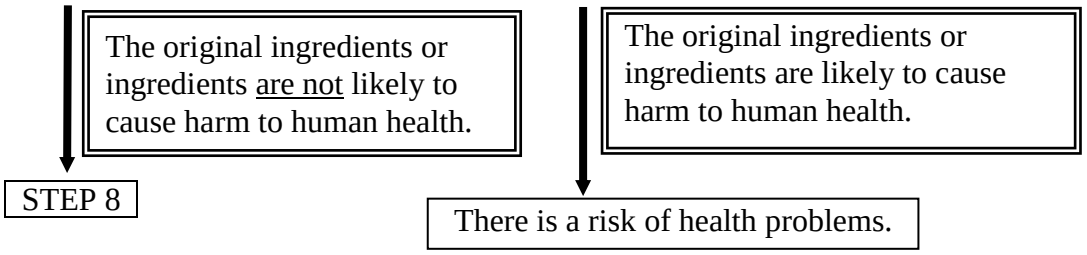
The research shows that the original ingredients do not contain alkaloids that are known as harmful substances, toxins, hormones, substances that effect on the nervous system, carcinogens, teratogens, genotoxins, other toxic substances, or their structurally-related substances.



STEP 7

Conduct safety studies using original ingredients or ingredients.[*12, *13]

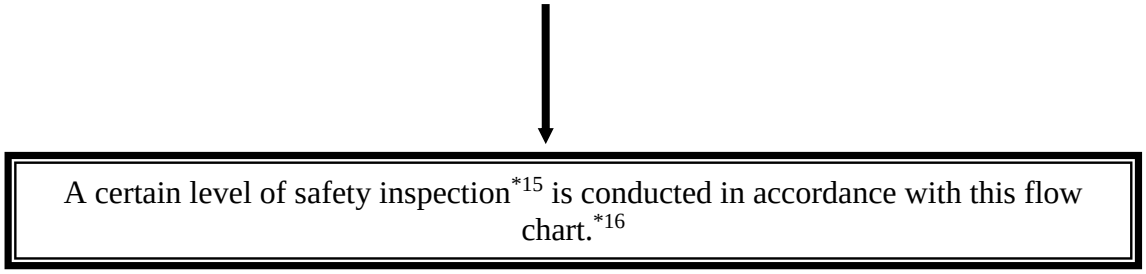
If time permitted, these studies should be conducted using standard methods with reference to the "Guidelines for designation of additives and revision of standards for the use of food additives," etc. However, repeated oral administration toxicity studies (preferably for duration of 90 days or more) or *in-vitro* genotoxicity studies can be conducted first. If the effects on human health cannot be determined with these study results, then, conduct long-term toxicity studies, *in-vitro* genotoxicity studies, or other appropriate studies to evaluate the results.



STEP 8 (Final stage)

Clarify the compounding ratio of all ingredients.

Thoroughly manage the hygiene of products*[14] and continuously collect safety information.



*1: The food additives for which use standards are established must be used within the range of the standards.

*2: Refer to the Guidance and Regulations on Unapproved/Unlicensed Pharmaceutical products (Notice of the Director-General of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, *薬発* No.476, June 1, 1971).*

* Available at the website of the Ministry of Health, Labour and Welfare (https://www.mhlw.go.jp/kinkyu/diet/dl/torishimari.pdf)

*3: It is desirable to assure the quality of original ingredients by profile analysis and morphological and DNA analysis; to implement voluntary GAP (Good Agricultural Practice); or to manage product traceability. When data of a product

that has been distributed as a pharmaceutical product is used, the ingredients to be used should be the same as that product in terms of the origins and used parts of individual original ingredients and the manufacturing methods of the ingredients.

*4: It is desirable to conduct manufacturing process management according to the voluntary practices, such as GMP (Good Manufacturing Practice).

*5: The ingredients equivalent to existing foods mean those that are in conventional food form, and that are recognized and socially accepted as food having a long history of consumption as food. Also, the intake of each ingredient should be equivalent to the amount ingested as food in conventional form.

*6: Cases of harmful effects include cases with likelihood of harmfulness.

*7: Examples of reasonable reasons: [1] It is scientifically shown that the harmful components are removed in the process of processing and manufacturing. [2] The components are already-known and the intake of each component is sufficiently within the range of safety in light of data.

*8: Conduct documentary research or experimental research of components contained in the original ingredients or the same part of the same animal/plant as the original ingredients or the individual animal/plant used as the original ingredients. Then, conduct documentary research of safety information on each component obtained in the survey, regardless of the origin of the original animal/plant.

*9: If there is no information on the components of the original ingredients, choose "No."

*10: If the research shows that the original ingredients contain a harmful substance, choose "No."

*11: Examples of reasonable reasons: [1] The safety of the components in question can be assured, for example, based on the history of its consumption as food. [2] In-depth safety studies have been conducted on the same original ingredient.

*12: Perform the studies based on the appropriate GLP (Good Laboratory Practice), such as the Standards for Implementation of Pharmaceutical Safety Studies. The study results should be published in academic papers and on websites.

*13: In the case of a single compound, the safety studies on a substance equivalent to the compound in question can be acceptable. "Equivalent" means that the substance corresponds to the compound in terms of all of the following: (i) origin, (ii) the manufacturing method, and (iii) purity. A safety study with an ingredient mixture is acceptable, if the mixture is of the same mixing ratio as the final product. In this case, however, it is not regarded as a safety study of a single ingredient.

*14: Product hygiene should be managed, for example, by analyzing impurities, such as heavy metals, or conducting microbial tests.

Also, it is desirable to manage manufacturing process according to voluntary practices, such as GMP.

*15: As mentioned in the main text, note that the safety of the tablet/capsule form foods cannot be assured only by conducting the safety inspection as given in the guidelines.

*16: Be aware that, for ensuring safety, it is critical to set an appropriate amount of consumption. Needless to say, it is desirable to perform safety studies on all ingredients.